

Clinical Applications of Diffusion/Perfusion MRI: A Review

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Introduction

This presentation will review how diffusion/perfusion MRI (D/P MRI) techniques have been employed for medically-relevant purposes. The focus will be on neurological applications because the brain is most often studied with these techniques, although neuroimaging has not been the only area of clinical application. Studies of cancer in the brain and elsewhere in the body are areas of growing clinical application. The clinical focus of the presentation will not permit a discussion of the rather large body of relevant “preclinical” studies that have been done in animal model systems. The presentation is meant to give only an overview. A comprehensive full scale review of the literature can not be achieved in the time allotted.

At the outset it is important to state that “clinical application” is actually a spectrum of activity. On one end of this spectrum is the routine everyday clinical use to solve diagnostic problems associated with treating individual patients. An example of this is Diffusion-Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) imaging, which are now used on an everyday basis in many hospital imaging centers for the diagnosis of stroke. At the other end of this spectrum lie clinical research applications. In these applications, D/P MRI may, for instance, be used to study a disease process in patients. The goal of such a research project may be to demonstrate that a D/P MRI is sensitive to some important feature of the disease process in a way that may ultimately lead to proving that D/P MRI can augment existing diagnostic tools for that disease. Given that D/P MRI provides a means of imaging certain physiological characteristics, an alternative goal may be to document how a disease process alters physiology. Also included in clinical research applications are clinical trials of new drugs or devices. Here the sensitivity of D/P MRI to physiological parameters allows it to provide biomarkers that can be useful to the goal of proving that the drug or device is effective and safe. For instance D/P MRI may provide biomarkers that subcategorize the disease process leading to the identification of certain populations of patients that may see enhanced benefit from the new drug or device. Biomarkers derived from D/P MRI may also provide a surrogate measure of outcome that may be helpful in understanding precisely how effective is the drug or device that is under study. The presentation will provide multiple examples taken from along this spectrum of clinical applications of D/P MRI.

It is also important state, as a matter of introduction, that there is a spectrum in the extent to which the various D/P techniques are available for clinical application. Essentially all manufacturers of clinical MRI systems, offer DWI and ADC imaging as parts of systems that are cleared for marketing by regulatory bodies such as the United States Food and Drug Administration (FDA). The dynamic T2*-weighted imaging techniques and the contrast agents used in Dynamic Susceptibility Contrast (DSC) perfusion MRI are also FDA-cleared and readily available in the clinical market place. At the other end of this spectrum lies Arterial Spin

Labeling (ASL) perfusion techniques. Thus far all investigations using ASL have been performed with custom written software that has not been FDA-cleared. Accordingly, ASL has not been used for routine everyday clinical purposes and there have been far fewer ASL studies in comparison with DWI, ADC and DSC studies. Diffusion Tensor Imaging (DTI) currently lies in the middle of this spectrum. Several MRI manufacturers offer FDA-cleared packages that allow the clinician or the clinical investigator to obtain DWI with specific directional sensitivity (although the number of directions tends to be limited) but no manufacturer offers FDA-cleared software that supports the diagonalization of the diffusion tensor at each image voxel or the more sophisticated DTI features such as directional color mapping or fiber tracking.

A final significant introductory point is that clinical diffusion applications are far more prevalent than are perfusion applications. This is almost certainly the result of three factors. The first is that diffusion techniques are much more easily implemented in clinical settings because they are readily available, relatively fast to perform and do not require the administration of contrast agent. Second, DTI is quite unique in its sensitivity to the ultrastructural features of cerebral white matter. There is essentially no other way to image these features on a large scale whole brain basis. Third, except for the specific case of ischemic disease, blood flow alterations are not a major feature of disease processes.

Stroke

The introduction of D/P techniques for assessment of acute stroke in patients occurred during the late 1990's. As a result, DWI and ADC imaging is now routinely used in many centers to assess patients who may have had a recent stroke. These techniques have the advantages of being fast and relatively easy to perform and can therefore be readily applied in acute stroke. Hyperintensity on DWI and/or reduced ADC is usually taken as a conclusive indication that a particular patient has had a stroke. While there are several characteristic problems of interpretation, such as "T2 shine through" in DWI, and a few alternative causes for elevated DWI signal (or reduced ADC), these imaging techniques are very powerful for the diagnosis of stroke. Their strengths are even further augmented by other MRI techniques, such as Magnetic Resonance Angiography (MRA) and Gradient Echo Susceptibility-weighted MRI, that can be performed in the same imaging session. In addition to identifying whether a particular patient has had a recent stroke, they are also quite effective at identifying the affected brain locations, the size of the affected area and whether there is salvageable brain tissue present.

Identification of the ischemic penumbra in acute stroke is an important research goal. The most clinically relevant definition of the penumbra is "tissue that is at risk, but still salvageable". In the diffusion-perfusion mismatch approach to identifying the ischemic penumbra, the diffusion abnormality identifies the core irreversibly injured tissue, while the perfusion abnormality identifies the tissue at risk of eventual infarction and the "mismatch" represents the penumbra. The mismatch concept is based on natural history studies of untreated patients in which early diffusion abnormalities were observed to grow over time into the area of the initial perfusion abnormality. However, several problems with the mismatch model have been raised. The first problem relates to differentiation of true penumbra from tissue experiencing benign blood flow attenuation associated with the stroke. The perfusion abnormality often overestimates the final infarct volume and the region of mismatch may overestimate the amount of tissue that is actually at risk. A second problem is the assumption that the initial diffusion lesion represents irreversibly infarcted tissue. Various studies have demonstrated that in humans, diffusion lesions may be reversed if blood flow is restored at an early time point. Based on these findings, more sophisticated approaches for identifying the penumbra have been proposed.

An important observation has been that significant mismatch may be present up to 24 hours or more from symptom onset, although the number of patients with mismatch progressively decreases over time. This provides evidence that the time window available for salvage of the penumbra in select patients may be much longer than the traditional 3-6 hour window. This has led to the concept of employing MRI to select patients for late reperfusion therapies.

There are several noteworthy methodological issues related to the evaluation of stroke either on an individual patient basis or within clinical trials. Neither the diffusion nor the perfusion techniques have been particularly sophisticated. Simple “3-direction” DWI tends to be used. The utility of fractional anisotropy (FA) and mean diffusivity (MD) as are derived from full scale DTI data acquisition has only been superficially explored in acute stroke, although there are a few clinical studies of chronic stroke in which DTI has been used to assess white matter degeneration that results from stroke. For acute stroke the longer imaging times and the more complex post-processing procedures are probably the key factors responsible for the far less frequent use of DTI for acute stroke. Similarly DWI with very high b-values is not routinely applied to acute stroke, although preliminary studies with stroke patients clearly show that the two b-values that are usually used do not fully characterize the diffusion compartmentation. Perfusion MRI of acute stroke has been almost universally performed with DSC MRI techniques. There have been only a few studies that have explored the use of ASL in acute stroke. Here the problem has been that blood delivery to the penumbra can be so slow that the spin label is lost to T1 relaxation before arrival in penumbral tissue. Furthermore the DSC-MRI postprocessing procedures have been relatively unsophisticated. The use of blood flow, blood volume and mean transit time image calculations is still relatively rare. Arrival time measures are the most frequently used approaches.

Tumors

Clinical roles for diffusion MRI in tumors have been under investigation since diffusion MRI became technically feasible for human studies in the 1990's. In general these potential roles include accentuation of the non-invasive diagnostic specificity of other MRI techniques and the provision of information useful for managing treatment. A central hypothesis that underlies these investigations has been that the quantitative imaging of the ADC (or MD) are inversely related to cell density and therefore that ADC imaging can assess the degree of cellularity/necrosis within tumors and their subelements. Various efforts with fractional anisotropy (FA) imaging have also been pursued based on the hypothesis that brain tumor tissue has a greater degree of microscopic disorganization compared with normal gray or white matter.

A number of small studies (typically less than 50 patients) have evaluated whether ADC, MD and FA imaging can distinguish neoplastic from non-neoplastic lesions (e.g. infectious lesions). Additional studies have explored whether these quantitative imaging approaches can distinguish tumor types and grades. These studies have yielded some statistically significant positive findings, but generally illustrate that diffusion MRI used alone is not sufficiently specific for diagnosis of individual patients.

There are several potential roles for diffusion imaging in treatment of cancer. The provision of unique surgical management information has been a focus of a number of studies. Several studies have suggested that the combined use of fMRI and DTI tractography can identify specific white matter fibers that are associated with eloquent cortical areas. Indices based on FA and MD have been developed to identify whether tumor has invaded nearby white matter. Efforts to assess whether quantitative ADC, FA and MD imaging can distinguish effective from

ineffective treatment and tumor regrowth have been performed in tumors in various parts of the body.

Tumors in the brain and other parts of the body have also been studied by perfusion imaging techniques. Most commonly, DSC-MRI is used. Here a specific goal has been to use blood volume images as means of identifying the relative amounts of cellular tumor and necrosis that are present in particular tumor subelements. There is also a substantial degree of current interest in using DSC-MRI measures as biomarkers in trials involving anti-angiogenic drugs.

Multiple Sclerosis

It has been known for many years that multiple sclerosis (MS) produces focal transient lesions throughout the white matter on T2-weighted MRI and contrast enhanced T1-weighted MRI. Furthermore there is evidence to suggest that there may be more widespread microscopic damage throughout the white matter that is associated with the ongoing inflammatory process and that is not detected with these traditional techniques. Accordingly, current research interests include using newer more sensitive MRI techniques such as D/P-MRI to detect and quantify the presence of inflammation throughout the white matter and possibly even in the gray matter. Accordingly several studies have focused on measurements of ADC and FA in the normal appearing white and gray matter of patients suffering from MS. Similarly measurements of resting perfusion in MS patients have been made to determine whether there are widespread perfusion abnormalities that may correlate with disease severity or predict the future appearance of focal lesions. The broader goal is to develop D/P-MRI biomarkers that may be useful for assessing treatment regimes.

Epilepsy

There has been recent interest in the use of D/P MRI techniques to characterize brain lesions that are associated with epilepsy. Studies of immediate postictal patients with ADC imaging have shown complex changes in the epileptogenic zone. In general ADC increases are present, but in a few cases ADC decreases have been observed. This is likely the result of the variability of seizure severity in terms of excitotoxic damage and the dynamic nature of physiological changes in the postictal state. Similarly ASL techniques have been used to demonstrate that perfusion abnormalities are present in the affected temporal lobe of patients suffering from temporal lobe epilepsy.

Other areas

D/P MRI has been applied in the studies of a wide range of other disorders including substance abuse, aging, dementia, traumatic brain injury, and neuropsychiatric disorders. In addition the techniques have also been used in studies of normal brain development.

Conclusion

There is a rich and complex literature that describes the clinical use of D/P MRI techniques. Stroke is currently the only condition for which D/P MRI is used on an everyday basis for routine clinical evaluations. Research studies have documented that D/P MRI is sensitive to other disorders. Studies that define how to interpret D/P MRI findings within the context of particular diseases are underway as are studies that define how to use D/P MRI biomarkers in clinical trials of drugs and devices. There is far more interest in diffusion techniques, particularly DTI, at the present time because they are relatively easy to perform in comparison to contrast-based perfusion techniques. There is certainly a larger role for ASL to

play because it measures perfusion without contrast administration, but use of ASL has been limited because it is not available as an FDA-cleared commercially available product.

Selected Further Reading

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